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Investigations into the deformability and tensile strength of pellets

Michael Salako, Fridrun Podczeck *, J. Michael Newton

Department of Pharmaceutics, The School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX, UK

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Abstract

The fracture and deformation properties of soft and hard pellets, which were prepared as described by Lundqvist et al. (1997), have been studied by measuring individual pellets and groups of pellets subjected to compaction in a punch and die system. Uncompacted, hard pellets were found to be less brittle and less deformable than soft pellets. However, the soft pellets were found to fracture under the influence of low tabletting pressures, and laser light reflection measurements have shown that they are able to form a coherent network of deformable material in tablets at higher tabletting pressures. Hard pellets were more resistant to crack propagation, but cracks and flaws were formed if a threshold tabletting pressure of about 9 MPa was reached. A change in the surface and internal pellet structure appears therefore certain. However, even under the influence of high loads the pellets were unable to deform to such an extent that a coherent network of material was formed in the tablets. Hard pellets differed from soft pellets by a factor of about 5 in their tensile strength, whereas they differed by a factor of 2 in their shear strength. Tested in tension, hard pellets had a higher strength value than the soft pellets, while when tested in shear they were characterized by the lower strength value. While compacts made from soft pellets were found to reduce their volume considerably under load, compacts made from hard pellets decreased in volume only slightly by deformation, but initially by particle rearrangement. This is a further sign of the larger deformability of the soft pellets in comparison to the hard pellets studied.

Keywords: Brittleness; Deformation; Pellets; Shear strength; Surface roughness; Tabletting; Tensile strength; Weibull-modulus

1. Introduction

Pellets are currently not used as a separate dosage form. Usually, a single dose of pellets is filled into a hard gelatin capsule. To increase the

* Corresponding author. Tel.: +44 171 7535857; fax: +44 171 7535942; e-mail: podczeck@cua.ulsop.ac.uk

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rate of production, efforts have been made to investigate the potential of manufacturing tablets from pellets (Béchard and Leroux, 1992; Lopéz-Rodrìguez et al., 1993; Aulton et al., 1994; Çelik and Maganti, 1994; Schwartz et al., 1994). A particular problem occurs if pellets are coated with polymer films to produce a slow but steady drug release with time. The tabletting process has often been found to cause severe damage to the film coating, so that the prolonged release from the resulting tablets could not be achieved. Mixing pellets with powder can result in segregation of the pellets producing non-uniform tablet composition.

To protect drug containing pellets from damage during tabletting and avoid segregation, Pinto et al. (1997) and Lundqvist et al. (1997) developed a system, in which the drug containing pellets were embedded in a certain ammount of soft pellets, which cushioned the drug pellets during the tabletting procedure, with the aim of minimizing damage of the drug containing pellets. In both works, the authors also included a third type of pellet to induce tablet disintegration. However, to date nothing is known about the physical properties of the soft and hard, drug containing pellets, so that the mechanism of tablet formation, cushioning and detailed requirements for the mechanical characteristics required from mixtures of these pellets, is not fully understood.

The aim of this work was to characterize two of the types of pellets used by Lundqvist et al. (1997) in terms of their physical properties in order to identify, how the proposed system worked.

2. Materials and methods

Soft and hard pellets produced by Lundqvist et al. (1997) were used in this study.

The tensile strength of the pellets was determined using a CT-5 (Engineering Systems, Nottingham, UK), instrumented with a 5-kg load cell. The pellets were strained until tensile failure occurred. When using pellets, the development of an internal tensile stress and a surface tensile stress have to be distinguished. Both types of stress develop at the same time and together lead to the tensile failure of the pellet when strained. The internal tensile stress is often approximated from an empirically established relationship (Hiramatsu and Oka, 1966; Darvell, 1990; Sikong et al., 1990):

$$\sigma_f(i) \approx \frac{0.7F}{\pi R^2} \tag{1}$$

where $\sigma_f(i)$ is the internal stress, F is the failure load, and R is the radius of the pellet. However, Eq. (1) becomes invalid, if the platens of the test system are so hard that their surfaces are not indented by the pellet, which is then the only entity that deforms during loading. In this case, the internal tensile stress is grossly underestimated (Hutchings, 1996). On the other hand, the surface tensile stress around the equator of the pellet is independent of platen deformation and thus is generally applicable (Shipway and Hutchings, 1993). This takes the form of:

$$\sigma_f(s) = \frac{0.4F}{\pi R^2} \tag{2}$$

where $\sigma_f(s)$ is the surface tensile stress. The advantage of the latter equation is also that it is based on a theoretical foundation, which has been proved to be valid experimentally, rather than being only an empirical relationship. In this study, therefore, the surface tensile stress was determined.

Pellets are brittle in nature, and hence their tensile strength is not invariable. Stanley and Newton (1977) have shown that Weibull-analysis (Weibull, 1951) is in such cases a useful tool to characterize a batch of nominally identical specimens. The Weibull-modulus m is a measure of the variability of the failure properties of a pellet batch and is indirectly proportional to the range of flaw sizes present in the brittle pellets, not to the absolute flaw size. The smaller the value of m, the more brittle the pellet. The value of the Weibull-constant x_o is a characteristic strength value of the pellet batch and quantifies the stress for 63.2% probability of failure. In this work, Weibull-analysis was performed using the numerical methodology described by Erck (1994). In this model, a further constant, x_u, is introduced into the model to account for deviations from perfect brittleness, i.e. a small degree of plastic deformation before failure occurs. The function used thus has the following form:

$$P(x) = 1 - e^{\frac{-[(x-x_u)^m]}{x_o}} \quad (3)$$

where $P(x)$ is the probability of failure ($P(x) = n_x/(N-1)$; n_x is the ranking of the pellet that failed at a tensile stress value of x) when N pairs of data are sorted in increasing order of x; x_u, x_o and m were defined previously. Linear regression of the following equation was used to determine the model parameters:

$$\ln(-\ln[1-P(x)]) = m \cdot \ln(x-x_u) - m \cdot \ln(x_o) \quad (4)$$

The goodness of fit of the data using Eq. (4) was measured using residual analysis and is here summarized with the value of the root mean square deviation.

The agglomerate shear strength (τ'_o) was obtained from the following relationship (Adams et al., 1994):

$$\ln P = \ln\left(\frac{\tau'_o}{\alpha'}\right) + \alpha'\epsilon + \ln[1-\exp^{-\alpha'\epsilon}] \quad (5)$$

where P is the compaction pressure, τ'_o is the agglomerate shear strength, α' is a pressure coefficient, and ϵ is the natural strain, i.e. the natural logarithm of the ratio between initial bed height and height of the compact at P. At higher compaction loads, the term $\ln[1-\exp^{-\alpha'\epsilon}]$ becomes very small and can be neglected, so that the value of τ'_o can be obtained from linear regression.

Ten grams of pellets were compacted in a 20 × 20-mm square split die using a Universal Testing Machine (Instron, Model TT, High Wycombe, UK) at different tabletting pressures applying a speed of 1 mm/min. The die could be disassembled to remove the compacted specimens.

The deformation of the pellets was visually inspected employing the following procedure. The top and bottom surface of the compacts was scanned with a laser beam (UBM laser profilometer, Ettlingen, Germany), and the reflection pattern of the surfaces was recorded. A 12 × 12-mm surface was always scanned, using 20 points/mm and a scanning frequency of 100 points/min. At the same time, the surface roughness of the compacts was determined. It is here represented as the average deviation of the roughness profile from a mean line (so-called rugosity, R_a), and the fractal dimension characteristic for the surface (FD). The roughness parameters are evaluated from 3-dimensional measurements. Hence, the value FD of a perfectly smooth surface should be 2, whereas the value of FD increases towards 3 with increasing surface roughness.

3. Results and discussion

The surface tensile stress of the hard and soft pellets was measured before and after tabletting. The first tabletting pressure used was small enough so that the compacts formed fell apart into single pellets, after the pressure was released and the die opened, but was high enough to cause visual deformation of the soft pellets. The second tabletting pressure led to formation of handable compacts, from which, however, single pellets could be obtained applying a small force between two fingers. All other pressures resulted in stronger compacts, from which individual pellets could not easily be obtained. Therefore, these pellets could not be used to measure their surface tensile stress. The results of the strength measurements are summarized in Table 1. Analysis of variance was employed to test the statistical relevance of the changes observed.

The application of a small pressure (2.89 MPa) to soft pellets did not significantly alter the surface tensile stress of the pellets, suggesting that deformation occurring did not cause major flaws inside the pellets. A small drop in the Weibull-modulus, however, was observed, which indicates that the pressure led to some cracks at the surface of the pellets. A further increase in tabletting pressure (5.99 MPa) was complemented by a significant drop in surface tensile stress, and the Weibull-modulus also dropped markedly. This comparatively low value of pressure therefore was able to cause failure of the pellets.

The surface tensile stress of hard pellets is more than five times larger than that of soft pellets. Uncompacted hard pellets have a higher resis-

Table 1
Tensile strength of pellets ($n=23$)

Pellet type	P (MPa)	$\sigma_f(s)$ (MPa)	m	x_o (MPa)	x_u	RMS (%)
Soft	—	0.22 ± 0.06	1.790	0.24	0.000	92.47
	2.89	0.21 ± 0.08	1.601	0.23	0.000	157.07
	5.99	0.15 ± 0.06	1.335	0.16	0.000	152.58
Hard	—	1.24 ± 0.18	4.286	1.34	0.003	51.90
	9.45	0.98 ± 0.33	1.934	1.14	0.000	67.13
	14.43	0.74 ± 0.42	1.189	0.80	0.000	175.26

m, Weibull-modulus; P, tabletting pressure; RMS, root mean square deviation (residual analysis); $s_f(s)$, surface tensile stress; x_o, characteristic pellet strength; x_u, plasticity term.

tance to fracture and are less brittle than soft pellets, as demonstrated by the larger value of the Weibull-modulus and the need to introduce a plasticity term (x_u) into the Weibull-function. The hard pellets are also less deformable, which can be seen from the compaction pressures required to produce compacts similar in mechanical strength to those made from soft pellets. The surface tensile stress is significantly different for all three sets of pellets studied, showing that, while the pellets initially are more resistant to pressure, they are more easily damaged, once a threshold pressure has been exceeded. The Weibull-modulus drops to half of its original value, which indicates the formation of numerous cracks and flaws at the surface of and presumably also inside the pellets. A change in the drug dissolution could therefore not necessarily be the result of film damage, but could be the consequence of a changed surface and internal structure of the pellet, which is more liable to allow fast drug dissolution.

During compaction, pellets are constrained to fail mainly in indirect shear due to a radial principal stress induced by neighbouring pellets (Adams et al., 1994). It is therefore also valuable to estimate the agglomerate shear strength. It was found that the agglomerate shear strength of the hard pellets (11.94 MPa) is only half of the value obtained for soft pellets (21.59 MPa). Therefore, the agglomerate shear strength was generally considerably higher than the tensile strength of the single pellets. Again, this confirms the brittleness of the pellets, and the difference between hard and soft pellets further proves that soft pellets are more brittle than hard pellets.

The laser light reflection patterns of some of the compacts produced are shown in Figs. 1 and 2. For soft pellets, the increase in tabletting pressure gradually causes the pellets to deform, so that single pellets are less distinguishable. At the highest tabletting pressure, a homogeneous surface has been formed. Using hard pellets, however, even at high tabletting pressures single pellets can still be readily identified. The pellets have not deformed sufficiently to contact each other over larger areas other than the equatorial zone. This agrees with the above conclusions that the hard pellets are less deformable than the soft pellets.

In this study, the assessment of the surface roughness of the specimens was undertaken using a spacing of 50 μm between each measuring point. This was done to evaluate the macroroughness of the compacts, which is a function of the pellet deformation, rather than the microroughness of individual pellet surfaces. The surface roughness of the compacts (Table 2) is therefore indicative of the deformability of the pellets. When comparing the classical surface roughness parameter R_a, it can be seen that for soft pellets, the surface roughness overall decreases with increasing tabletting pressure. Even at the highest tabletting pressures this effect is clearly visible. Hence, these pellets deform gradually over the whole cross-sectional area. However, for hard pellets, the surface roughness appears not to change systematically. This is due to the high resistance to deformation of the pellets. The pressure range used was insufficient to overcome this resistance. Hence, under tabletting conditions similar to those used by Lundqvist et al. (1997), namely 30–40 MPa, pellet deformation could be prevented if the pellet mixture contained soft pellets, which would give way to the hard pellets under pressure and at the same time form a percolating network of deformable material. However, this

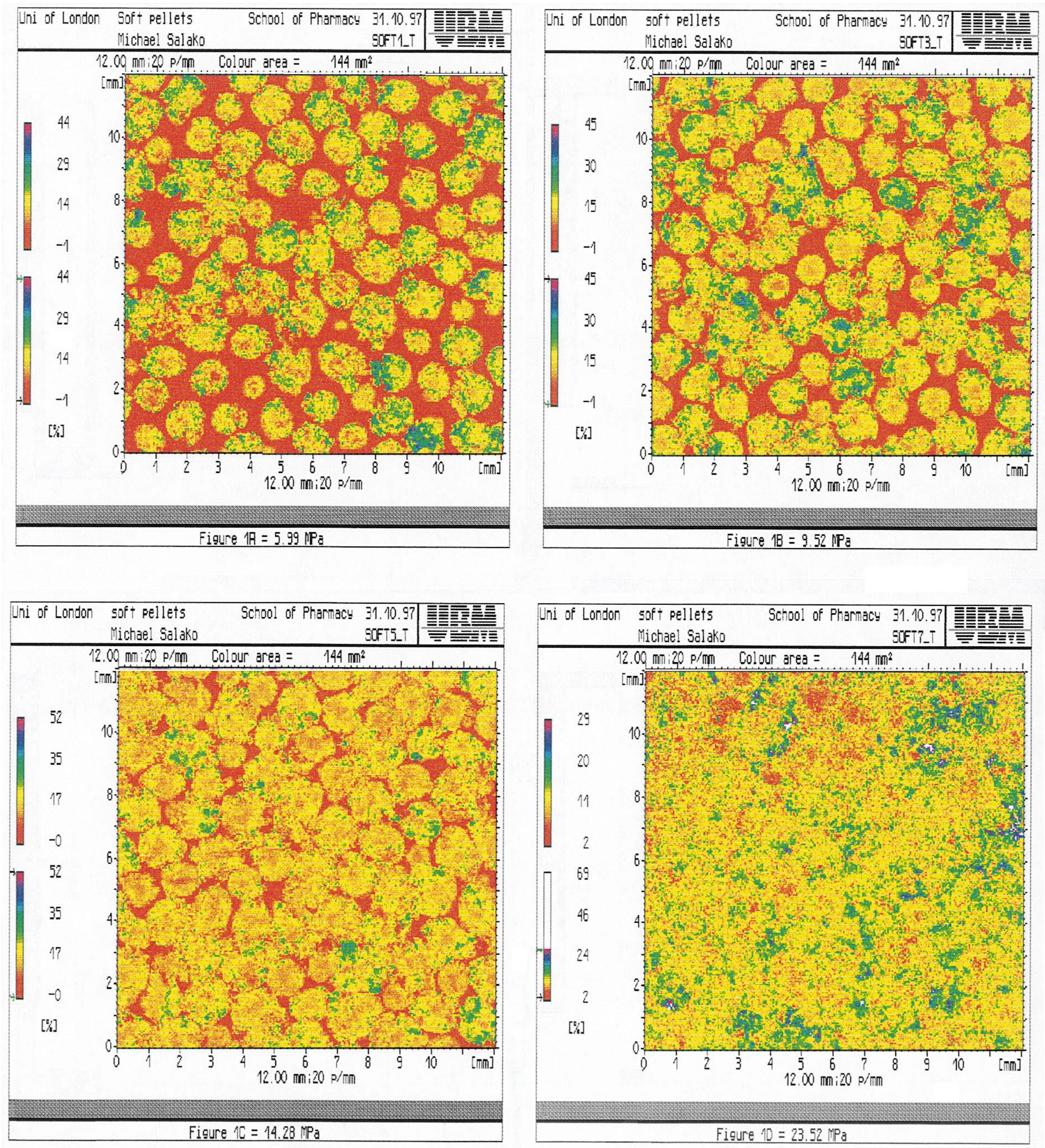

Fig. 1. (*Caption overleaf*)

also means that a minimum content of soft pellets is needed to prevent damage of the hard pellets under load. This percolation threshold appears to lie at 40% of soft pellets (Lundqvist et al., 1998). Thus, a restriction in using this technology appears to be the amount of hard pellets for a single dose, because the tablet weight and consequently tablet volume will nearly double due to the minimum amount of soft pellets needed. Therefore, this technology will be restricted to low and medium dose drugs.

Comparing the surface roughness of the upper and lower faces of the compacts, it can be seen that the roughness of the lower surface in most cases provides the higher values. This indicates that the compaction stress has not been fully transmitted from the upper to the lower punch. Apparently, the soft pellets do not transmit the stress completely, because large amounts of energy are consumed by deformation. Using hard pellets, the results indicate that at the lowest pressure (14.43 MPa) no important deformation took place, and the volume reduction was simply due to particle rearrangement (similar surface roughness for upper and lower compact face). In the pressure range between 17.31 and 24.53 MPa, the hard pellets deformed, and consequently the stress was not transmitted completely. Therefore, the surface roughness of the lower compact faces was higher. Using 29 MPa and more, the surface roughness again took on similar values for the upper and lower compact faces. Hence, the main deformation process had ended at about 29 MPa, and further pressure led mainly to an increase in elastic deformation.

When comparing the fractal dimensions of the surfaces, no clear pattern can be obtained with respect to changes in surface roughness. For macroroughness studies it appears therefore that this roughness parameter does not reflect the characteristic properties of the surfaces.

Finally, the deformability of the pellets can be judged by comparing the height of the specimens after unloading, which reflects the degree of deformation which has occurred. Different tabletting pressures were required to form the compacts, so that only some of the compacts of the soft and hard pellets can be compared. For example, soft pellets compacted at 14.28 MPa can be compared with hard pellets compacted at 14.43 MPa. While the height of the former compact had reduced by 21%, the height of the compact made from hard pellets had at this tabletting pressure reduced by 30%. Thus, initially hard pellets are able to reduce more in volume without bond formation, i.e. by particle rearrangement. This might be due to their strength, which prevents particle damage under load. A further increase in tabletting pressure to 23.52 MPa (soft pellets) and 24.53 MPa (hard pellets), however, decreased the compact height by 13 and 6% of the previously achieved height for soft and hard pellets, respectively. Hence, an increase in compaction load reduces the volume of soft pellets steadily, while the height of the hard pellets compact decreased comparatively less, and therefore hard pellets can be classified as less deformable than soft pellets.

4. Conclusions

Soft pellets when prepared as described by Lundqvist et al. (1997) fracture under the influence of low tabletting pressures and form a coher-

Fig. 1. Laser light reflection pattern of compacts made from soft pellets, upper surface; compaction pressure: 1A = 5.99 MPa; 1B = 9.52 MPa; 1C = 14.28 MPa; 1D = 23.52 MPa. (Laser light reflection patterns depend on two separate features of the surface, which are the differences in surface height, i.e. the variability in distance between the surface and the initial position of the light source, and the surface micro- and nano-roughness. The colours representing these features can be chosen and have been set here as follows: red for deep cavities and groves, which are the result of an incomplete contact between the individual pellets, and which provide only limited reflection; yellow for the highest areas of the surface, i.e. undeformed parts of the pellets sticking out, which due to surface roughness provide a medium level of laser light reflection; spectrum from green over dark blue to purple for the highest areas of the surface when deformation of the pellets has occurred. Deformed pellets have a lower surface roughness and therefore provide a larger laser light reflection than undeformed pellets. The full scale and extent of reflection can be seen from the colour bar and the corresponding percentage reflection on the left hand side of each picture. The maximum extent of light reflection depends on the initial travel distance of the laser, which cannot be controlled by the operator, and is hence of variable magnitude.)

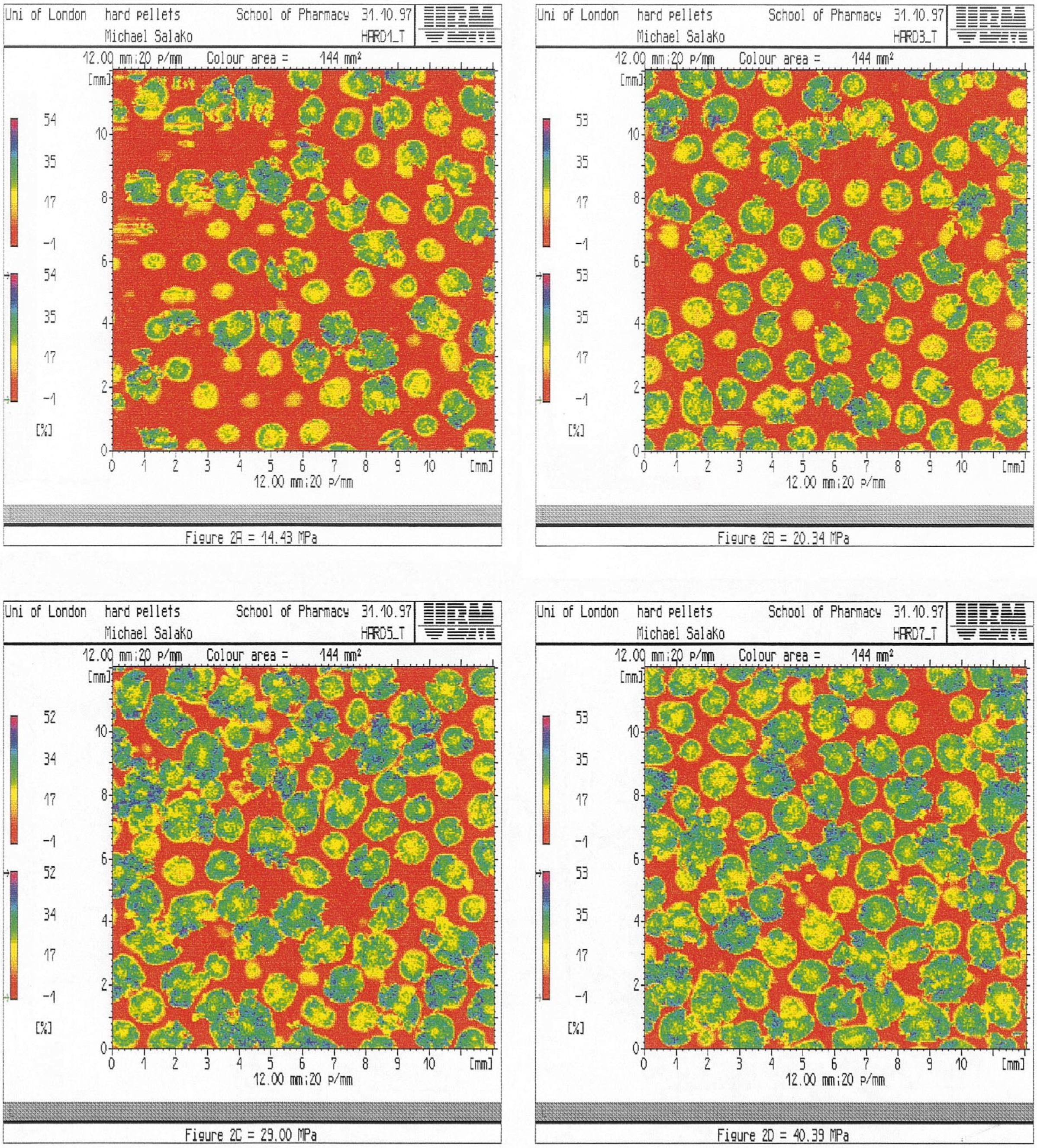

Fig. 2. Laser light reflection pattern of compacts made from hard pellets, upper surface; compaction pressure: 2A = 14.43 MPa; 2B = 20.34 MPa; 2C = 29.00 MPa; 2D = 40.39 MPa. (For a general interpretation of the colour spectrum refer to Fig. 1. The pronounced occurrence of green and blue areas suggests that the micro- and nano-surface roughness of the hard pellets, even when undeformed, is smaller than that of soft pellets. However, the increased red area due to cavities and groves implies that the pellets as a whole are less deformed and have formed less contact between each other.)

Table 2
Compaction pressure and surface roughness of the compacts

Pellet type	P (MPa)	Upper compact face		Lower compact face	
		R_a (μm)	*FD*	R_a (μm)	*FD*
Soft	5.99	5.67	2.392	7.23	2.388
	7.65	4.28	2.386	5.93	2.358
	9.52	3.67	2.380	6.51	2.357
	11.69	3.62	2.406	5.87	2.341
	14.28	3.23	2.372	5.85	2.366
	17.31	3.13	2.384	5.31	2.314
	23.52	2.74	2.392	5.91	2.367
Hard	14.43	8.50	2.432	8.45	2.472
	17.31	6.66	2.409	11.50	2.412
	20.34	6.93	2.425	9.20	2.402
	24.53	7.38	2.422	10.64	2.435
	29.00	8.40	2.397	8.83	2.380
	33.47	8.94	2.399	7.85	2.407
	40.39	7.74	2.374	8.66	2.356

FD, fractal dimension; P, compaction pressure; R_a, rugosity.

ent network of deformable material in tablets. Hard pellets are more resistant to crack propagation, but cracks and flaws are formed if a threshold tabletting pressure is reached. Thus, for example, a change in drug dissolution properties as reported, for example, by Pinto et al. (1997) could be due to the change in the surface and internal pellet structure. Assuming a mixture of both types of pellets, it appears as though a coherent network of soft pellets could prevent such damage, but only if it is formed at tabletting pressures below the critical value for the hard pellets, or if a sufficient amount of soft pellets is added to cushion the hard pellets during application of load. For the studied set of soft and hard pellets, the critical tabletting pressure appears to be at about 9 MPa, while the sufficient amount for cushioning lies according to the literature (Lundqvist et al., 1998) at about 40% of soft pellets.

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